UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/857,826	06/07/2001	Y. Tom Tang	PF-0637 USN	2342

27904 7590 02/24/2005

INCYTE CORPORATION
EXPERIMENTAL STATION
ROUTE 141 & HENRY CLAY ROAD
BLDG. E336
WILMINGTON, DE 19880

EXAMINER
TURNER, SHARON L

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 02/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 10/03)

Office Action Summary	Application No.	Applicant(s)	
	09/857,826	TANG ET AL.	
	Examiner	Art Unit	
	Sharon L. Turner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-28,31,32,41 and 42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-28,31,32,41 and 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *21-28,31,32,41 and 42* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10-26-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Response to Amendment

1. The amendment filed 10-26-04 has been entered into the record and has been fully considered.

2. The Examiner notes the previous receipt of three separate declarations under 37 CFR 1.132 by John Coughlin Rocket III, Vishwanath R. Lyer and Todd Bedilion.

The declarations were previously considered but were not persuasive to overcome the rejections of record. In particular, the declarations did not provide evidence of patentable utility within the context of 35 USC 101 for the claimed invention.

3. The Examiner acknowledges receipt of various references as noted in the 10-26-04 response.

4. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

5. As a result of Applicant's amendment, all rejections not reiterated herein have been withdrawn by the Examiner.

Priority

6. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows: The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the

requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

In particular, priority is not found within the 60/198,234 application filed December 11, 1998 for the sequences of SEQ ID NO:17 and 44 to which the claims are drawn.

The Examiner notes that support within the disclosure of the 60/119,365 application, filed February 9, 1999 is found. In particular '365 SEQ ID NO:4 is 100% identical to instant SEQ ID NO:17. '365 SEQ ID NO:19 is 100% identical to instant SEQ ID NO:44. The specification of the '365 application is similar, but differs in that the disclosure is directed to nervous system associated proteins (NSASP) in contrast to neuron associated proteins (NEUAP).

To obtain the full benefit of the February 9, 199 application, the disclosure must meet all patentability requirements with respect to 35 USC 101 and 112.

Instant specification has been rejected for a lack of utility and lack of enablement. Accordingly full benefit is not provided and the effective filing date awarded instant claims is that of instant filing date of 6-7-01. If utility is established at the time of filing and is supported by the largely cumulative disclosure of the 60/119,365 application, then the effective filing date may be adjusted accordingly.

In the response of 10-26-04 Applicants argue that the specification sets forth sufficient utility and enablement for the claimed invention in accordance with

the statutes and that therefore the effective filing date of the 60/119,365 priority document should be awarded.

Applicants arguments filed 10-26-04 have been fully considered but are not persuasive for the same reasons as set forth below under the noted rejections for each statute.

Election/Restriction

7. Applicant's election with traverse of Group XVII corresponding to new claims 21-28, 31 and 32 in the Paper of 10-14-03. The traversal is on the ground(s) that claims 38-40 are drawn to antibodies and compositions, depend from the elected invention and are interrelated to the same special technical feature and thus should be examined together. In addition Applicants argue that all claims are so related and represent minimal burden for examination, see arguments pp. 8-12. Applicants request rejoinder based upon allowable subject matter. These arguments are not found persuasive. In particular, the special technical feature polynucleotide and peptide lack unity as noted in the art of record. Moreover, the inventions define unique special technical features and distinct methods of using the distinct technical features as disclosed and claimed. In accordance with PCT Rules the invention thus lacks unity and is separable.

The requirement is still deemed proper and is therefore made FINAL.

8. Claims 29-30 and 33-40 are canceled.

9. This application contains newly presented claims 41-42 drawn to the elected invention.

Claim Rejections - 35 USC § 101

10. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

11. Claims 21-28, 31-32 and 41-42 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial, credible asserted utility or a well established utility.

The specification discloses at pp. 1, lines 1-5 that, "This invention relates to nucleic acid and amino acid sequences of neuron-associated proteins and to the use of these sequences in the diagnosis, treatment and prevention of cell proliferative disorders including cancer, neuronal and neurological disorders, and autoimmune/inflammation disorders." In particular, the specification references at least 27 unique peptide sequences termed NEUAP proteins for neuron associated proteins, see in particular pp. 7, lines 25-34. As noted in the specification at pp. 9, lines 30-31, "Table 2 shows features of each polypeptide sequence, including potential motifs, homologous sequences, and methods, algorithms. and searchable databases used for analysis of NEUAP." In Table 2 under the column "Identification", with respect to SEQ ID NO:17, the Table states "bipolar disorder- associated protein (g2271473)." Yet the specification provides no further detailed information as to the data referred to therein and its relationship to bipolar disorder. The specification contemplates multiple laundry lists of uses in relation to the disease noted at pp. 33-34 and 43-44 but fails to exemplify any specific and substantial use of the claimed nucleic acids and/or

protein encoded thereby. In particular, the significance of the molecule, its functions, effects and specific and substantial utility are lacking. While the specification contemplates the various reagents as useful in various molecular techniques of experimentation, such utilities are not specific or substantial because the uses merely rely on the inherent properties of any nucleic acid to hybridize (bind) and/or encode and any peptide to bind and/or stimulate an immune response. Thus, the disclosed nucleic acids and peptides merely constitute research reagents for further experimentation to discover their "real-world" use. The contemplated uses also do not constitute well-established utilities because their functional significance has yet to be established. The peptides are merely disclosed as being neuron-associated peptides. But there is no known sequence structure or function disclosed or recognized as being related to any of a multitude of neurological or neuron associated functions. In addition, the specification does not teach any conserved nucleic or amino acid positions critical to neuron activity, function or phenotype. As recognized by Skolnick et al., Trends in Biotech., 18(1):34-39, 2000, the skilled artisan is well aware that there is an unpredictable nature in the ability of encoding nucleic acids to predict structural and functional activities for any particular protein or protein family, and that even when highly homologous and conserved residues are known only experimental research can confirm the artisan's best guess, see in particular Skolnick, abstract and Box 2. Thus, the assignment of instant SEQ ID NO: 17 as a neuron associated protein and the brief mention of it's identification in Table 2 as a bipolar disorder associated protein fails to define

either a specific or substantial asserted utility or well-established utility for the claimed sequences.

Applicants traverse the utility rejection of record as set forth in pp. 8-33 of the 5-6-04 response.

Applicant's arguments filed on 5-6-04 at pp. 8-33 have been fully considered but are not persuasive.

In particular, Applicant's argue that the NEUAP-17, bipolar disorder-associated protein is an encoded gene expressed in humans, that it is a member of the class of neuron-associated proteins whose biological functions include neuronal signaling (with reference to p. 1) and that as such the invention has numerous practical uses in toxicology testing, drug development, and the diagnosis of disease, none of which require knowledge of how the polypeptide actually functions. However, the disclosure at p. 1 fails to delineate how NEUAP-17 provides specific and substantial asserted utility or well established utility in neuronal signaling, toxicology testing, drug development, diagnosis of disease or information as to how the peptide actually functions.

Applicants argue that NEUAP-17 is homologous to GenBank g2271473 described as associated with neuronal disease bipolar disorder (a presumed known undisputed utility) (with reference to Table 2, p. 68) and assert that the two polypeptides share more than 67% identity over 250 amino acid residues. Applicants argue this homology is reasonable probability for utility to be imputed, with support via Brenner. However, neither Yoshikawa et al., Am. J. of Med. Genetics (Neuropsychiatric Genetics) 74:140-149, 1997, Yoshikawa et al.,

Genomics 47 (2), 246-257 (1998) nor GenBank Accession g2271473 evidence specific and substantial asserted or well established utility for NEUAP-17 or any particular use in bipolar disorder. Yoshikawa et al., 1997 notes a putative chromosome 18 localization for bipolar disorder. Yet the relevant linkage of genes and localization with respect to NEUAP-17 are not established. Yoshikawa et al., 1998 notes transciptional variants with LDLRA and transmembrane domains involved in binding calcium and LDL. However, the reference fails to establish specific and substantial asserted utility or well established utility for NEUAP-17 as claimed. While there is significant homology, the noted homology is not associated with any specific and substantial asserted utility or well established utility.

Applicants assert direct proof of utility via the Rockett, Bedilion and Iyer declarations in addition to noted scientific references. Applicants assert that such evidence establishes utility within the art as useful in expression analysis, in particular to drug discovery efforts detecting expression of proteins, encoding transcripts or antibodies. Applicants assert evidence that the biological function of the gene need not be known for usefulness, that each additional target probe is even more useful, and that failure to detect is not evidence that negates any probes usefulness. However, the evidence is insufficient to establish specific and substantial asserted utility or well established utility for NEUAP-17 as claimed. The Rockett and Lyer declarations evidence methods of analyzing (detecting) gene, protein or antibody expression as a research tool to discover particular patterns, relationships or correlations. However, usefulness of any

sequence as a research tool, or a means of approaching scientific discovery, fails to evidence specific and substantial asserted utility or well-established utility for the sought NEUAP-17 sequences as claimed. The Rocket, Lyer and Bedilion declarations further note that each additional probe is even more useful as a research tool and means for discovering expression, patterns, relationships or correlations. While each new sequence is indeed a member of the broad generic class and may be added as a research tool or means for discovery in expression analysis, such addition fails to evidence specific and substantial asserted utility or well established utility for the claimed sequences of NEUAP-17. Use as a research tool in experimental testing fails to evidence specific and substantial asserted or well established patentable utility. Moreover, while such reagents are valued, as noted in Bedilion and Lyer, as research tools in comparison testing or expression experimentation, such value fails to evidence specific and substantial utility or well established utility for claimed NEUAP-17 seqeunces. Further while the noted references evidence various research strategies utilizing expression studies, such references fail to evidence specific and substantial asserted utility or well established utility for NEUAP-17 of the claims. It is true that one may conduct research with the probe regardless of whether the research assay provides for positive or negative results. Yet conducting research is not a specific and substantial asserted utility within the context of 35 USC 101. Such assays are well established in the art, yet the contribution is not provided by experimental testing, it is provided by the completion of results which attach specific meaning or significance to the findings such that the artisan can

use a specific assay in a specific way with predictable outcome the is noted to provide for beneficial effect.

Applicant's direct comments to the applicable legal standard of utility with cited case law as at pp. 12-13 of the response. Accordingly Applicant's assert that the use in toxicology testing, drug development and diagnosis of disease are sufficient to meet 35 USC 101 and 112, first paragraph. Applicants further assert that such provides credible and well-established utilities for the claimed invention.

The Examiner has not rejected the invention as being un-credible under Patent Law. However, the asserted utilities are akin to usefulness as a research tool and in research discovery testing which are not deemed by the Office to be specific and substantial asserted utilities or well-established utilities within the context of 35 USC 101. Mere placement of the reagent probes within the broad generic class of biological molecules useful in experimental research expression testing or as a research tool, fails to evidence patentable utility meriting award for the completion of an invention. As in *Brenner v. Manson*, "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." Hence, these arguments and evidence are not persuasive.

Applicants assert that similarity to g2271473 provides undisputed utility with reference to publications 19, 20 and Brenner et al., because the NEUAP-17 is structurally and functionally related to g2271473, (65% identity over 250 amino acids). Applicants assert the Examiner must accept such assertion absent evidence or sound scientific reasoning of doubt. Applicants assert that Skolnick

fails to contradict Brenner. However, the Examiner does dispute this conclusion. First it is noted that the function of the g2271473 sequence is not established. Similarly function for instantly claimed NEUAP is not disclosed or established in the art. While the g2271473 sequence is identified as a bipolar disorder associated protein, such identification is based upon the description of Yoshikawa as an expressed cDNA encoding a peptide located on the chromosome within a region near a region described as having a potential role in bipolar associated disorder. Yet, neither the function of the g2271473 nor the NEUAP-17 sequence is established as related to bipolar disorder. Importantly, Yoshikawa et al., 1997 suggests a putative chromosome 18 localization for bipolar disorder. Yet the relevant linkage of genes to bipolar disorder and their localization have yet to be established, see in particular Yoshikawa et al., 1997, p. 140-141. Yoshikawa teaches the "detection and mapping of 48 chromosome 18-specific, brain expressed cDNAs, about half of which represent unique sequences encoded by novel genes." Yoshikawa is a suggestion to research such sequences as potential candidates for their possible linkages to bipolar disorder, but falls short of linking the gene as causative or related to such disease. Accordingly utility for either g2271473 or NEUAP-17 is not established with respect to bipolar disorder or otherwise. While the alignment does establish that the proteins are related structurally, the alignment fails to teach the artisan how to use either the g2271473 or the related NEUAP-17 sequences to provide benefit. Applicants apparently impute that because the proteins are related structurally that they are related functionally. This may be true. However, and

more importantly, neither reference teaches specific and substantial asserted utility or well established utility for either protein sequence. Yoshikawa et al., 1998 notes transcriptional variants with LDLRA and transmembrane domains involved in binding calcium and LDL. However, such disclosure fails to establish specific and substantial asserted utility or well established utility for either g2271473 or NEUAP-17 as claimed. Skolnick and Brenner are relevant to determining the predictability of structural and functional similarities amongst particular sequences. Yet in instant case no specific or substantial property is noted to be provided based upon the noted similarity and therefore neither specific and substantial asserted utility nor well established utility is provided. The localization of NEUAP-17 is not noted to be at chromosome 18 or linked to bipolar disorder, it merely shares homology to a sequence disclosed as a possible putative candidate as it is localized to a region on the chromosome which may be relevant to disease. As noted by Yoshikawa, there would be relatively thousands of genes in the noted region, yet none of them are causally linked even though all of the may be identified as preferred targets for experimentation designed to determine if any single one of them are in fact linked to bipolar disorder, see pp. Yoshikawa et al., 1997, pp. 140-141.

Applicants assert utiltiy via toxicology testing, drug discovery and disease diagnosis as practical uses that confer "specific benefits" to the public via protein expression profiling as described in Rockett, Bedilion and Lyer declarations. Applicants assert there is no dispute that the claimed invention is a useful tool in two-dimensional PAGE analysis and western blots to monitor protein expression

and assess drug toxicity. Applicants note filing data for instant case. Applicants note 2-D PAGE analysis for protein expression testing and as used in toxicology and drug efficacy testing. Applicant notes the Rockett declaration and various assertions therein. Rocket concludes that the disclosure of any new sequence of a peptide would be sufficient information for use of such in profiling studies. Further the Bedilion is noted to provide that one of skill in the art would similarly understand the use for any polynucleotide in monitoring cDNA expression or as in the declaration via Lyer, that such uses provide for maximum versatility as a research tool when each identified gene is used as a probe. While such declarations speak to the desire to use the noted reagents within the broad generic class of all expressed nucleic acids or peptide sequences, research use testing is not recognized as a specific and substantial asserted utility or well established utility within the context of 35 USC 101. Research use testing is not the completion of an invention, but a desire to seek out the relevant significance or benefit which may be provided. The invention is not complete until the experimentation identifies a specific result that is placed within the context of meaning. Here no end result or significance is established based upon any research use testing. It is a search to discover and not a description of its completion.

Applicant assert that the use of polypeptides expressed by humans as tools for toxicology testing, drug discovery and the diagnosis of disease is now "well established." Applicants point to various references utilizing such experimentation, see in particular, References 12-15. The Examiner does not

dispute that such assays are used in the art as a means of conducting experimentation. Applicants assert that Patent references 1 -2, 5 and 7-9 evidences that utility is well established for all expressed polypeptides and polynucleotides in toxicology testing, see in particular noted citations at pp. 17-25 of the response. Applicants note the potential benefits to the public of having the expressed sequences for expression research testing as noted at pp. 25-26 of the response. Applicants assert that the Examiner failed to address or consider these "well established" utilities and that the rejection should be overturned regardless of merit.

In response the Examiner acknowledges that expression analysis is a well established tool for experimental research testing. However, the specification fails to note completion of such testing to reveal any particular finding or significance for the peptides or nucleic acids. Instead Applicants offer that the newly disclosed polynucleotides or peptides can be used in such analyses and thus that this possibility of testing provides for patentable utility within the context of 35 USC 101. However, as previously noted, the subject of research testing is not in and of itself evidence of specific and substantial asserted utility or well established utility within the context of 35 USC 101. The Examiner has considered this proposed use, but found it to fall short of the standard. There is no provision for overturning the rejection regardless of merit.

Applicants further assert that objective evidence corroborates the utilities of the claimed invention via real world evidence. In particular, Applicants argue that the sale of such novel sequences on gene chips for experimental research

testing evidences real world utility. In particular Applicants refer to reference 16 as providing for further acknowledgement of drug discovery processes evidencing the value of such sequences when used in such research methodology. These arguments are not persuasive as noted above. Research experimentation is not recognized as completion of an invention, regardless of potential benefit. The utility is not one of a specific and substantial asserted utility or well established utility without completion of such research to arrive at findings that place the artisan in possession of particular significance, for example linkage to a disease or drug effect.

Applicants assert the Examiner's rejections are without merit, that the precise role or function is not required of utility and offer various case law as well as evidence noted in the Rockett, Bedilion and Lyer declarations. However, the Examiner does not require such as a sole basis for rejection. It is merely offered as one noted defect amongst others. Applicants offer that the uses of NEUAP-17 in toxicology testing, drug discovery and disease diagnosis are practical uses beyond mere study. Applicants offer the peptide as a tool for research and attempt to distinguish this from research merely to study itself, an object of research. This argument has been fully considered but is not persuasive because as previously noted the basis for this argument lies in providing utility based merely upon its placement in the broad generic class of all biological proteins and is not considered specific and substantial as asserted or well established.

Applicants argue that no evidence demonstrates that the artisan would reasonably doubt utility of the claimed invention. These arguments are addressed as above via Yoshikawa et al., 1997 and 1998 references. Skolnick is no ore deficient or proficient in its teachings than Applicants Brenner. Both evidence unpredictability in function based solely on homology comparisons. Yet further, utility is not established as noted via the references and therefore, even if one acknowledges that the two peptides bear homology, such does not evidence a specific and substantial asserted utility or well established utility for either the related g2271473 sequence or for instant NEUAP-17.

Applicants argue that the Examiner and the Utility Guidelines and Training Materials misstate the law in requiring Applicant to assert a particular or unique utility. In response, the requirement is not that Applicants provide a "particular or unique" utility. The Guidelines and Training Materials are used as guidance. The analysis of the noted specific sequences within context of the specification and prior art fails to evidence patentable utility within the context of 35 USC 101. No completion of such research experimentation testing is provided where significance for the sequence or its expression is established. Moreover, as previously noted no other significance or context of use evidences completion of an invention by the artisan. The sequence provided without more is not determined to be of patentable use.

In the response of 10-26-04, Applicant's further argue that instant sequences are disclosed at pp. 32-33 as being useful for the diagnosis, treatment or prevention of cell proliferative disorders including cancer and useful

for treating disease associated with decreased expression such as prostate cancer, lymphoma and leukemia. Applicant's note that SEQ ID NO:17 is 99% identical to the literature recognized TMEPAI/PMEPAI and that Xu et al., Cancer Res., 2003, 63:4299-04 (10-26-04 IDS) and Rae et al., Mol. Carcin., 2001, 32:44-53 (10-26-04 IDS) note decreased expression of these homologous sequences exhibit decreased expression in prostate tumor cells, exhibit inhibitory effects on cell growth when over-expressed in androgen dependent or independent CaP cells and that expression was not detectable in leukemia and lymphoma cells. Accordingly, Applicants assert that at lease one credible, specific and substantial assertion of utility was provided via the specification that is sufficient to overcome the utility and enablement requirements.

Applicants arguments filed 10-26-04 have been fully considered but are not persuasive. The Examiner notes that applicants statements as to utility referred to at pp. 32-33 of the specification are amongst an entire host of generic contemplations concerning the polynucleotide and polypeptide's prophetic use in a laundry list of diseases. Applicants then assert that specific post-filing date experimental findings evidence utility and enablement for the claimed sequences in the diagnosis and treatment of prostate cancer, leukemia and lymphoma. Yet, the noted references do not teach such end results and further the specifics noted therein were not disclosed via the specification as originally filed. Therefore the Xu and Rae references do not evidence completion of an invention at the time of applicants filing, but in contrast evidence experimentation and discoveries critical to pathologies as noted therein. For example, Xu's findings

are specific to primary highly androgen-induced and androgen treated CaP prostate cancer cells. Xu demonstrates that PMEPAI through its PY motifs interacts with WW domains of the human NEDD4 protein and that in CaP cell lines conferred cell growth inhibition and at lease one of the PY motifs of PMEPA1 *may* be involved in its cell growth inhibitory functions. Xu suggests further experimentation to discocver a link in expression between lossed or reduced expression in CaP and a role in prostate tumorigenesis. In essence, Xu, is not completion of an invention but and invitation for further experimentation, and the teachings are limited to CaP cell lines. Yet even so, instant specification fails to teach even these minimal elements and hence the suggestion for the criticality of such linkage is not specifically evidenced via the specification. Further with respect to Rae, this reference notes an upregulation in renal cell carcinoma, as well as normal expression in prostate and ovary. Upregulation was also noted in stomach and rectal adenocarcinomas but was barely detectable in lyeukemia and lymphoma. At most, Rae suggests that the up-regulation of this gene *may* play an important role in tumorigenesis. Yet, similar to Xu, such does not evidence completion of an invention for linkage analysis and further fails to evidence particular use in diagnosis or treatment of leukemia or lymphoma when expression was barely detectable. Hence, the noted references fail to evidence specific and substantial utility at the time of filing for particular findings which were not disclosed in the specification and which fail to even evidence themselves completion of an invention with in the context of the noted statutes. Rejection therefore is maintained.

Claim Rejections - 35 USC § 112

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 21-28 and 31-32 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial, credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

In addition to the aforementioned, the following defects are noted with respect to enablement of instant invention as claimed, even if utility should be found.

14. Claims 21-28, 31-32 and 41-42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Applicants amendment of 10-26-04 introduces the language "having decreased expression in leukemia, lymphoma and prostate tumor cells" and note support at pp. 23-24 of the specification.

However, support for such recitations are not specifically found within pps. 23-24. Accordingly the recitation constitutes new matter absent evidence for support.

15. Claims 21-28, 31-32 and 41-42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specifications disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without undue experimentation. The factors relevant to this discussion include the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims.

Applicants claims are directed to peptides with greater than single amino acid substitutions, naturally occurring variants, biologically active peptide fragments and immunogenic fragments.

The specification does not enable the broad scope of the claims which encompasses a multitude of analogs or equivalents because the specification does not teach which residues can or should be modified such that requisite functionality is maintained, note utility rejection above. The specification provides essentially no guidance as to which of the essentially infinite possible choices is likely to be successful in any particular use and the skilled artisan would not expect functional conservation amongst homologous sequences. Thus,

applicants have not provided sufficient guidance to enable one skilled in the art to make and use the claimed derivatives in a manner reasonably correlated with the scope of the claims.

As to "naturally occurring", "90%" and "biologically active" variants, the skilled artisan recognizes that nucleic and amino acid alterations may lead to differences in function. For example, the skilled artisan recognizes as noted in Skolnick et al., above and as further exemplified by Choh, PNAS 77(6):3211-14, 1990, that one or more amino acid deletions, insertions or substitutions including truncations results in unpredictable effects in the resulting biological molecule, its' biological function, the ability to bind and/or exhibit similar immunoreactivity. The specification teaches no structural or functional activities of a NEUAP protein or nucleic acid, fails to teach any residues which may be exchanged while retaining requsite activity or function and fail to teach the significance or function of any particular variants. As to the nucleic acids, the skilled artisan recognizes that encoding nucleic acids are dependent upon the structural nucleotides and their relationship to the genetic code and translational signals. The specification fails to note those nucleic acid molecules that are naturally occurring and capable of encoding the requisite peptides. As noted above the peptide structures and their pertinent sequences are insufficiently disclosed and/or enabled to the full scope of the claim.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made and still maintain activity/utility is

unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int. 1986). Thus, the skilled artisan cannot readily make and use the claimed sequences without further undue experimentation.

Applicant's amendment deleting "biologically active fragments" obviates rejection on these grounds. Applicants argue in the 5-6-04 response that sufficient guidance as to 90% variants is provided at pp. 13-14 of the specification and at pp. 17-18 with respect to hybridization conditions such that the artisan can make and use the invention. Applicants argue that such description is sufficient to chemically describe the genus, that the genus is not highly variant and that the state of the art allows for sufficient knowledge to ascertain the noted members.

Applicant's arguments submitted 5-6-04 have been fully considered but are not persuasive. The stringency conditions are not provided and neither is any functional property of the 90% variable molecules as recited. Accordingly, the experimentation required is undue as the artisan is not equipped with any means for ascertaining those molecules falling within the scope of the claims that exhibit similar function and/or use such that the species members bearing such structure define a genus capable of similar use. No functional property is recognized based upon hybridization testing and the members falling within the genus cannot be definitively tested without appropriate hybridization conditions which vary within the art. Further, structural similarity alone is insufficient to ascertain peptide function. No function is noted for NEUAP-17. Thus, there can

be no assurance via research testing or otherwise that any molecule having 90% similarity or hybridizing thereto, would more likely than not define a proper genus, sharing both structure and function. Rejection on the aforementioned grounds is maintained.

Applicants argue in the 10-26-04 that the noted claim amendments obviate the enablement rejection on the noted grounds. Applicants amendment has canceled the language "naturally occurring" from the claims. Rejection based upon this language is therefore obviated. Applicants amendment newly inserts the language "and having decreased expression in leukemia, lymphoma and prostate tumor cells" in relation to 90% and 95% identical sequences as in newly amended/presented claims 21, 28 and 41-42. However, Applicants specification and referral to the post-filing date references of Xu and Rae fal to evidence or establish sufficient linkage analysis or teachings to enable diagnostic or treatment applications using the noted sequences. Importantly, the specification fails to evidence that decreased expression of the noted sequences is definitively linked causative, resultive or prognostic to any disease, including leukemia, lymphoma or prostate tumor. The specification provides no scientific or experimental evidence of such uses. Moreover, as noted above, Xu and Rae further fail to evidence such definitive linkage or the specifics of any prognostic or diagnostic testing associated with decreased expression in leukemia, lymphoma and prostate tumor. Moreover, such linkage is not evidence for any sequence either 90 or 95% identical to instant sequences and an encoding strand may bear no association to others capable of of encoding a protein or any relation to a

genetically isolated allele. Applicants further referral to the structual features in Table 2 noting potential motifs, methods of comparing homology, signal peptide region, glycosaminoglycan attachment site and transmembrane region lend no information as to how the claimed invention or related sequences may be used to provide specif and substantial utilitly and enablement to any use in prognostic, diagnostic or treatment benefit with any relationship to decreased expression in leukemia, lymphoma or prostate tumor.

Accordingly Applicants arguments filed 10-26-04 have been fully considered but are not persuasive for the reasons set forth above.

16. Claims 21-28, 31-32 and 41-42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification describes NEUAP polypeptide sequences including that consisting of SEQ ID NO:17, but for which no functional significance or activity is described. The specification also notes the coding nucleic acids of SEQ ID NO:44 but fails to note any other functional significance of the nucleic acid sequence. The claims encompass polypeptides comprising fragments and homologues, i.e., polypeptides that vary substantially in length and amino acid composition. In particular, the language of the claims is directed to "naturally occurring", "90%" and "biologically active" variants.

The instant disclosure of a single polypeptide, that of SEQ ID NO:17 with no instantly disclosed specific activities, does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera. A genus claim may be supported by a representative number of species as set forth in Regents of the University of California v Eli Lilly & Co, 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), which states:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention". Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1980) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.") Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d 1565, 1572, 41 USPQ2d at 1966.
>
> An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id at 1170, 25 USPQ2d at 1606."

A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence,

falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. The instant specification discloses, however, a single isolated polypeptide sequence, that of SEQ ID NO: 17 and no other amino acid sequences that are proposed to possess the same activity, that are noted as being naturally occurring or that are disclosed as exhibiting any conserved biological acitivity or function.

Given the unpredictability of homology comparisons as noted above, see in particular Skolnick et al., and Choh et al., and the fact that the specification fails to provide objective evidence that any other additional sequences are indeed species of the claimed genus it cannot be established that a representative number of species have been disclosed to support the genus claim. No activity is set forth for the additional sequences. The specification further sets forth a proposed consensus sequence for the genus (90%) identity, yet there is no correlation or nexus provided between possession of this structural feature and any encompassed function of SEQ ID NO:17 such that it is clearly conveyed that possession of any polypeptide having this structural region, any part thereof or percent similarity in common would possess any defined activity or function. Thus, the claim recitations as to naturally occurring, 90% and biologically active variants and/or fragments lacks adequate written description support.

Applicant's amendment deleting "biologically active fragments" from the claims obviates rejection on these grounds. Applicants argue in the 5-6-04 response that the structural requirement of 90% without more is sufficient written description support for the artisan to determine those members encompassed by

the claims. Applicants further point to guidance from the specification at pp. 8, 23-24, and Tables 1-2 for characteristics of the genus. Yet no such characteristics are claimed and any such characteristic referenced in the specification cannot be imported into the claims. As previously noted 90% homology or hybridization alone is not sufficient to predict that any member sharing such characteristics would be similarly useful. No functional property is recognized based upon hybridization testing and the members falling within the genus cannot be definitively tested without appropriate hybridization conditions which vary within the art. Further, structural similarity alone is insufficient to ascertain peptide function. No function is noted for NEUAP-17. Thus, there can be no assurance via research testing or otherwise that any molecule having 90% similarity or hybridizing thereto, would more likely than not define a proper genus, sharing both structure and function. Applicant's arguments have been fully considered but are not persuasive. Rejection on the aforementioned grounds is maintained.

Applicants argue the written description rejection in the 10-26-04 as essentially noted above for the enablement requirement. In particular Applicants argue that the claim amendments obviate the written description rejection. Applicants amendment has canceled the language "naturally occurring" from the claims. Rejection based upon this language is therefore obviated. Applicants amendment newly inserts the language "and having decreased expression in leukemia, lymphoma and prostate tumor cells" in relation to 90% and 95% identical sequences as in newly amended/presented claims 21, 28 and 41-42.

However, Applicants specification and referral to the post-filing date references of Xu and Rae fal to evidence or establish sufficient linkage analysis or teachings to enable diagnostic or treatment applications using the noted sequences. Importantly, the specification fails to evidence that decreased expression of the noted sequences is definitively linked causative, resultive or prognostic to any disease, including leukemia, lymphoma or prostate tumor. The specification provides no scientific or experimental evidence of such uses. Moreover, as noted above, Xu and Rae further fail to evidence such definitive linkage or the specifics of any prognostic or diagnostic testing associated with decreased expression in leukemia, lymphoma and prostate tumor. Moreover, such linkage is not evidence for any sequence either 90 or 95% identical to instant sequences and an encoding strand may bear no association to others capable of of encoding a protein or any relation to a genetically isolated allele. Applicants further referral to the structual features in Table 2 noting potential motifs, methods of comparing homology, signal peptide region, glycosaminoglycan attachment site and transmembrane region lend no information as to how the claimed invention or related sequences may be used to provide specif and substantial utilitly and enablement to any use in prognostic, diagnostic or treatment benefit with any relationship to decreased expression in leukemia, lymphoma or prostate tumor. In conclusion, with respect to written description, Applicants specification fails to provide a single species member that is definitively linked to a particular function much less a sufficient number of species sufficient to describe a genus of sequences bearing a 90-95% identitiy which

would be reasonably expected to provide the artisan with additional members sharing any same function, significance or effect.

Accordingly Applicants arguments filed 10-26-04 have been fully considered but are not persuasive to provide written description support for the reasons set forth above.

Claim Rejections - 35 USC § 102

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

18. Claims 21-22, 24-28, 31-32 and 41-42 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent Application Publication No.: US 2003/0027998 filed March 2, 2001 and published February 6, 2003.

Publication 0027998 teaches novel genes encoding proteins having prognostic, diagnostic, preventative, therapeutic and other uses as noted, see in particular Abstract and pp. 1-205 specification. The sequence of SEQ ID NO:56 of the 0027998 publication bears 100% similarity with instant SEQ ID NO:17. Instant SEQ ID NO:44 bears 90.6% similarity with SEQ ID NO:55 of the 0027998 publication and bears 100% similarity within the coding sequence region, i.e., differing only in the non-coding upstream and downstream regions. In particular,

residues 101-1061 of instant SEQ ID NO:44 are 100% identical to residues 6-966 of 0027998 SEQ ID NO:55. The 0027998 reference further teaches the nucleic acids within vectors, host cells and methods of producing the polypeptide with encoding sequences, see in particular pp. 13-14184-188 and claims. Pharmaceutical compositions with excipient are noted at pp. 188-190. Thus, the reference teachings anticipate the claimed invention.

Applicants argue in the 5-6-04 response that the noted priority documents were not provided. This argument has been fully considered but is not grounds for obviating rejection as set forth. The Examiner need not provide such non-provisional documents as a requirement for rejection. Applicant may obtain copies of particular priority documents as provided for under 37 CFR 1.11 and 1.14. Rejection on these grounds is maintained.

Applicant's argue in the response of 10-26-04 that the effective dates provide priority to the Feb., 9-1999 application, that utilty and enablement are provided and that hence the 2003/0027998 and '130 patent are not prior art.

Applicant's arguments filed 10-26-04 have been fully considered but are not persuasive. Applicant's specification fails to teach specific and substantial utility, the ability to make and use the invention within the enablement requirement and therefore priority is not established. Thus, the art rejections are maintained for the same reasons of record. The property of having decreased expression in leukemia, lymphoma and prostate tumor cells are claimed as an inherent property to the sequence. To the extent that the sequence is anticipated, the prior art is necessarily enabling to the limitation.

Applicants arguments filed 10-26-04 have been fully considered but are not persuasive for the reasons set forth above.

19. Claims 21-22, 24-28, 31-32 and 41-42 are rejected under 35 U.S.C. 102(e) as being anticipated by Srivastava et al., US 6,566,130 20 May 2003.

Srivastava et al., teach androgen regulated gene expressed in prostate tissue, see in particular Title. The nucleic acids and peptides are noted to be useful in the diagnosis and prognosis of prostate cancer as evidenced by increased expression in androgen sensitive tumors, see in particular column 31-32. The peptide of the '130 patent, SEQ ID NO:3 bears 100% homology to instant SEQ ID NO:17 and the patent discloses all nucleotides capable of encoding the amino acid sequence, see in particular columns 4-5, vector comprising promoter and host cell for expression, see also columns 9-11. Pharmacuetical compositions comprisied of excipient are noted including isolation from media as in column 19-20 or nucleic acids in hybridization buffer as noted in Example 3 or 6. Thus, the reference teachings anticipate the claimed invention.

Applicant's arguments filed 10-26-04 have been fully considered but are not persuasive. Applicant's specification fails to teach specific and substantial utility, the ability to make and use the invention within the enablement requirement and therefore priority is not established. Thus, the art rejections are maintained for the same reasons of record. The property of having decreased expression in leukemia, lymphoma and prostate tumor cells are claimed as an

inherent property to the sequence. To the extent that the sequence is anticipated, the prior art is necessarily enabling to the limitation.

Applicants arguments filed 10-26-04 have been fully considered but are not persuasive for the reasons set forth above.

Status of Claims

20. No claims are allowed.

21. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

22. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (571) 272-0894. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached at (571) 272-0961.

Sharon L. Turner, Ph.D.
February 21, 2005

SHARON L. TURNER, PH.D.
PATENT EXAMINER